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Spontaneous Splenic Rupture as Manifestation of the Immune Reconstitution Inflammatory Syndrome in an HIV Type 1 Infected Patient with Tuberculosis

The immune reconstitution inflammatory syndrome (IRIS) is associated with the initiation of highly active antiretroviral therapy (HAART) in HIV-infected patients [1, 2]. The spectrum of clinical presentations ranges from a worsening of opportunistic infection under treatment to the atypical appearance of an unrecognized opportunistic infection to autoimmune disorders, such as Graves' disease [3]. Paradoxical responses during treatment for *Mycobacterium tuberculosis* (MTB) infection in non-HIV-infected patients had been recognized even prior to the advent of HAART [4, 5]. Clinical worsening in these patients was attributed to the reversal of MTB infection-induced immunosuppression and associated with the conversion of MTB skin tests from negative to positive [6]. In accordance with these assumptions, such patients were found to show improved pathogen-specific immune responses, based on delayed hypersensitivity testing or more advanced T cell techniques [4, 7]. However, deregulation of specific T cell responses has also been reported [8]. A rapid improvement of cellular immunity against specific antigens due to HAART may lead to symptomatic systemic inflammation. Consequently, anti-inflammatory treatment is required in severe cases of IRIS, which are potentially fatal, especially when the nervous system is involved [9, 10].

A 36-year-old native of Thailand presented to the emergency room with shortness of breath and fever lasting for 14 days. HIV infection with a CD4 count of 102 cells/ μ l had been diagnosed 3 years earlier. Antiretroviral treatment consisting of lopinavir/ritonavir, zidovudine and lamivudine was initiated at that time, and within 6 months the viremia was suppressed and the CD4 count increased to 300 cells/ μ l. One year later, he interrupted antiretroviral treatment and was lost to follow up. On admission, his temperature was 39 °C, blood pressure, 102/73 mmHg, pulse, 120/min, and frequency of respiration, 24 breaths/min. Physical examination of the transsexual man with silicon-breast implants showed normal clinical findings. Laboratory tests revealed an elevated level of C-reactive protein (CRP) of 167 mg/l, and normocytic anemia with a hemoglobin count of 5.4 g/dl; the plasma HIV RNA level was 469,000 copies/ml and the CD4 count 9 cells/ μ l. A chest CT scan showed diffuse bilateral infiltrates, and a bronchoalveolar lavage (BAL)

specimen revealed *Pneumocystis jirovecii* infection. Treatment with trimethoprim-sulfamethoxazole was started without steroids because of a pO_2 of 11 kPa. One week later, cultures for MTB from sputum and BAL samples were reported to be positive. Histological examination of a fine needle aspirate obtained from a mediastinal lymph node showed necrotizing, caseating granuloma with a high load of Ziehl-Neelsen-stained acid-fast bacilli. Antituberculous treatment with isoniazid, rifampicin, ethambutol, and pyrazinamid was started (day 7 after admission). The patient recovered rapidly and became afebrile; pulmonary oxygenation normalized, CRP normalized to 5 mg/l, and the hemoglobin level rose to 8.9 g/dl 2 weeks after starting antituberculous therapy (day 21). At this time it was decided to initiate HAART with lamivudine, zidovudine, and nevirapine. This early time point to start HAART was chosen in order (1) to optimize the complex antimicrobial therapies during the hospital stay, (2) to control for drug interactions, and (3) to guarantee treatment adherence of the homeless patient.

Ten days after initiating HAART (day 31) relapsing fevers recurred twice daily with temperatures of up to 40 °C, cutaneous lesions were noticed (tuberculide), and the patient fell short of breath again. Repeated blood, urine, and stool cultures remained negative for

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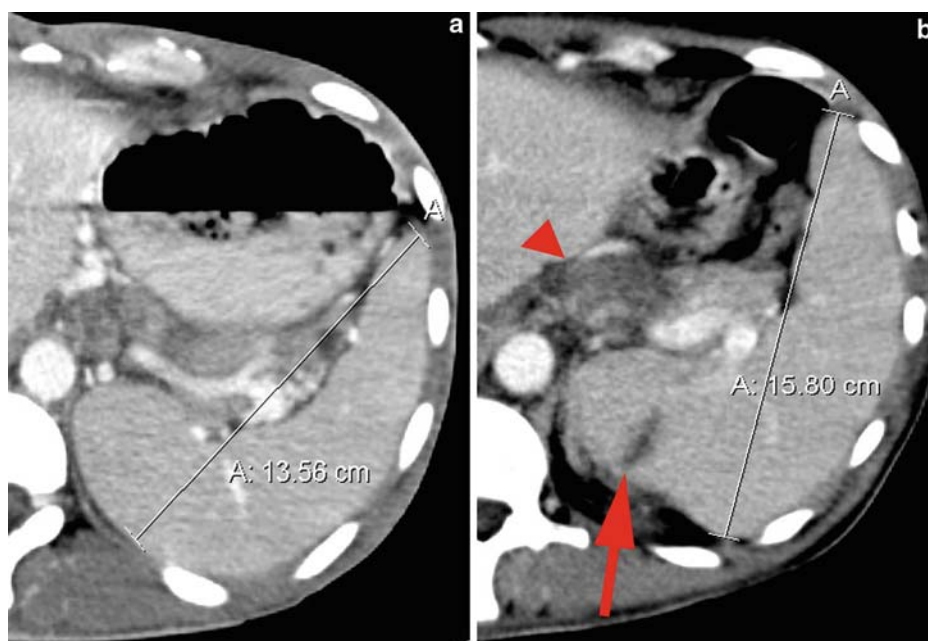
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additional microorganisms, and chest X-ray revealed no new infiltrates; the CRP was 335 mg/l. A diagnosis of IRIS was postulated and, subsequently, a therapy with prednisone 50 mg per day was started. The rise of the initial CD4 count of 9 (6%) to 45 (29%) cells/ μ l on day 31 within only 10 days of HAART was accompanied by a drop in the viral load from 469,000 to 894 copies/ μ l and strongly supported the diagnosis IRIS. Three days after starting prednisone (day 34) and without any trauma in the meantime, the patient complained of strong abdominal pain localizing in the left upper quadrant and of modest diarrhea. A contrast-enhanced abdominal CT scan demonstrated an increase of splenomegaly to 15.80 cm, which had been already present in the CT scan on admission (13.56 cm), and further enlargement of the mediastinal and abdominal lymph nodes, whereas the size of the liver did not change. Importantly, splenic rupture without active bleeding and without splenic abscess was diagnosed (Figure 1). Due to this potentially life-threatening condition, the patient was monitored for 24 h in the intensive care unit under strict bed rest: blood pressure remained stable around 100/70 mmHg, and hemoglobin was regularly measured at a level of 9 g/dl. The platelet count was $298 \times 10^3/\mu$ l and the international normalized ratio (INR) was 0.9, excluding a coagulopathy or bleeding tendency. Splenectomy was considered together with visceral surgery consultants, but it was deferred due to the stable clinical evolution and the substantial risks of the low immune status of the patient. Treatment with prednisone, HAART, and antituberculous drugs for presumable disseminated tuberculosis was continued. After 3 days, the patient was painless, but continued to be febrile, and a follow up CT scan showed no changes in the

size of the spleen (15 cm, day 37) or the splenic rupture. One month after the diagnosis of splenic rupture (day 67), the patient was afebrile, doing well, and was discharged on 15 mg prednisone, HAART (zidovudine, lamivudine, nevirapine), and antituberculous treatment with rifampicin and isoniazid. Another CT scan 8 weeks later (day 123) showed reversion of splenomegaly back to a baseline of 12 cm and disappearance of the signs of splenic rupture.

IRIS in HIV-infected patients treated for MTB infection was first described in the mid-1990s, when HAART became widely available. IRIS usually occurs within the first 2–3 months after initiation of HAART, with a median interval to the onset of symptoms due to MTB infections or cryptococcosis of 11 days [11]. However, rarely it can be diagnosed after 1 or 2 years of therapy. The questions of whether the occurrence of IRIS is related to the time between initiating treatment for an underlying opportunistic infection and starting HAART and when to start HAART optimally are still a matter of debate [2, 12]. However, it has been shown that the vast majority of MTB-related IRIS occurs within the first 4 weeks of the initiation of HAART [13, 14]. An increase of respiratory symptoms has been reported in patients with IRIS under treatment for HIV and MTB [15, 16], and paradoxical clinical worsening has been reported to have occurred in about 35% of patients [7, 17]. The presentations include prolonged fever, augmented cough or shortness of breath, hepatosplenomegaly, lymphadenopathy, and the development of cutaneous lesions and ascites. Most of these clinical findings are common and were also present in the case under discussion here. However only two cases of splenic abscess and rupture as

Figure 1. (a) Contrast-enhanced transverse CT of the abdomen showing the size of the spleen (13.6 cm) on admission. (b) Contrast-enhanced transverse CT of the abdomen on day 34 showing splenomegaly (15.8 cm), with a low-density linear area stretching centripetally from the capsule typical for splenic rupture (arrow) as well as necrotizing retroperitoneal lymphadenopathy (arrowheads). No evidence of bleeding or free fluid in the abdomen was present.



a consequence of IRIS and MTB infection have been described in the literature to date [18, 19]. In both cases, the spleen was removed and MTB infection was discovered in the specimen. In one case, splenectomy was performed upon demonstration of intraperitoneal blood by paracentesis; in the other case, the removal of the spleen was a preventive procedure. Following multidisciplinary evaluations, we decided to follow a conservative procedure in our case because of the absence of acute bleeding and/or sepsis, the relatively small size of the rupture, the surgical risk of this immunocompromised patient, and the patient's stable hemoglobin, blood pressure, and clinical presentation. The spleen was most likely infected by MTB in the context of disseminated tuberculosis, although infection was only formally demonstrated in the lymph node and the lung; nevertheless, we strongly believe that the reason for the observed spontaneous splenic rupture was the rapid increase in size of the spleen following the initiation of HAART. Interruption of HAART was taken into consideration but finally rejected because of the stable clinical situation.

In summary, splenic rupture represents a rare complication of a MTB infection related to IRIS in HIV-infected patients [20]. Whereas splenectomy was performed in two previously published cases of splenic rupture, our patient represents the first case successfully managed without splenectomy. In conclusion, the occurrence of abdominal pain in an HIV-infected patient with IRIS should provoke imaging to exclude splenic rupture that is potentially rapidly fatal.

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